

REMARKS

The present application is directed to pharmaceutical compositions containing a biologically active agent that is capable of generating a protective immune response in an animal and a polycationic carbohydrate, wherein the polycationic carbohydrate is a water-soluble alkylated chitosan with an increased degree of quaternization. Claims 1, 3, 5-6, 11-17, 20-22, 37 and 40 are pending. Claims 2, 4, 7-10, 18-19, 23-36 and 38-39 are cancelled. Claims 1 and 3 are currently amended. Claim 40 is new. Support for the amendments is found throughout the specification, and no new matter is introduced. In light of the following remarks, favorable consideration of the present application is respectfully requested.

Claim objections

In the Non-Final Office Action mailed October 3, 2006, the Examiner objected to Claims 18-19 and 36 under 37 C.F.R. 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully submit that Claims 18-19 and 36 are cancelled herein. Therefore, the claim objections are moot in view of applicants' amendment. Accordingly, applicants respectfully request withdrawal of the objections under 37 C.F.R. 1.75(c).

Claim rejections under 35 U.S.C. §102(b)

In the Non-Final Office Action mailed October 3, 2006, the Examiner rejected Claims 1 and 3 under 35 U.S.C. §102(b), as being anticipated by Kotze *et al.* (*International J. of Pharm.*, 1997) (hereinafter "Kotze"). Applicants respectfully submit that amendments to the claims overcome the rejection.

Claim 1 has been amended to clarify that the composition comprises a **biologically active agent** capable of generating a **protective immune response** in an animal and a polycationic carbohydrate. Additionally, applicants have defined that when the polycationic carbohydrate is trimethyl chitosan, the polycationic carbohydrate possesses a degree of **quaternization** that is at least **20%**. Support for the above amendment can be found on, at least, page 7, lines 13-21 and Example 3 of the published application. Specifically, Figure 2 indicates that mucosal co-

administration of trimethyl chitosan **possessing 60% or 40% quaternization** augmented the humoral response for F1 and V above and beyond that generated by buffer or underivatized trimethyl chitosan. Applicants respectfully submit that Kotze fails to teach or suggest a polycationic carbohydrate with at least 20% quaternization as claimed in the amended claims.

Furthermore, applicants respectfully submit that Kotze fails to teach or suggest a composition comprising a biologically active agent that is capable of generating a protective immune response. Accordingly, applicants believe they have overcome the Examiner's rejection under 35 U.S.C. §102(b) and request its withdrawal.

Claim rejections under 35 U.S.C. §103(a)

In the Non-Final Office Action mailed October 3, 2006, the Examiner rejected Claims 1, 3-4, 6, 11-18 and 36-37 under 35 U.S.C. §103(a), as being unpatentable over Kotze in view of Eyles *et al.* (hereinafter "Eyles"). Applicants respectfully submit that the amendments to the claims overcome the rejection.

As explained above, Kotze fails to teach or suggest a polycationic carbohydrate, wherein the polycationic carbohydrate possesses a degree of **quaternization** that is at least **20%**. Furthermore, Kotze certainly fails to teach or suggest a composition comprising a **biologically active agent** capable of generating a **protective immune response** in an animal and a polycationic carbohydrate possessing at least **20% quaternization**.

Applicants submit that one of ordinary skill in the art based on the teachings of Kotze would not be motivated to derive a composition comprising a polycationic carbohydrate of at least 20% quaternization because Kotze discloses that a trimethyl chitosan with **40-60% quaternization is unsuitable as an absorption enhancer** because the hydroxyl groups of the chitosan show a high extent of methylation. As a result, Kotze utilizes a trimethyl chitosan possessing **12.28% quaternization** (see page 1199, "Results" column entitled, "Synthesis and Characterization of TMC", last 7 lines of paragraph). Applicants respectfully submit that Kotze teaches one of ordinary skill in the art that a composition comprising a polycationic carbohydrate possessing greater than 13% is **undesirable** because such a composition would be **unsuitable**. Applicants believe that one of ordinary skill in the art based on the teachings of Kotze would not,

therefore, be motivated to combine a biologically active agent that is capable of generating an immune response in an animal with a polycationic carbohydrate with at least 20% quaternization, as claimed in the amended claims.

Claims 3, 6, 11-17 and 37 depend directly or indirectly on Claim 1. Accordingly, applicants submit that Claims 1, 3-4, 6, 11-18 and 37 are non-obvious in view of the prior art. As discussed above, applicants respectfully submit that the compositions of the instant application are novel and non-obvious over the teachings of Kotze. Furthermore, the deficiencies of Kotze are not satisfied by Eyles for at least the following reasons.

Eyles fail to teach a polycationic carbohydrate, wherein the polycationic carbohydrate possesses an **increased** degree of **quaternization**. In contrast, applicants direct the Examiner to Example 3 of the instant application wherein compositions comprising at least 20% quaternization were observed to augment the humoral response to F1 and V via intranasal administration.

Furthermore, Eyles provide no teaching or motivation to one of ordinary skill in the art to make a polycationic carbohydrate possessing at least 20% quaternization. Moreover, there is no motivation or suggestion to make a polycationic carbohydrate possessing at least 20% quaternization and a biologically active agent that is capable of generating a protective immune response in an animal, as claimed in the amended claims.

Applicants submit that, even if one of ordinary skill in the art were to combine Kotze and Eyles, which applicants do not concede, it would **not** lead the skilled person to arrive at the claimed invention because Eyles teach that biologically active agents (F1 and V antigens of *Y. pestis*) are stabilized by microencapsulation. Applicants submit that Kotze deals with improved absorption of therapeutic drugs and **teaches away** from using chitosans with greater than 13% quaternization, and Eyles discloses stabilization of vaccine antigens. Clearly the disclosures address different technical problems and, as such, there would be no motivation for one of ordinary skill in the art to combine the teachings without the benefit of hindsight. Even so, the fact that Kotze **teach away** from chitosans with a degree of quaternization greater than 20% means that a combination of the teachings would **not** lead to the claimed composition. As stated above, neither Eyles or Kotze teach or suggest the claimed composition. Accordingly, applicants

submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Non-Final Office Action mailed October 3, 2006, the Examiner rejected Claims 1, 3-6, 11-12, 16, 18-21 and 36-37 under 35 U.S.C. §103(a), as being unpatentable over Kotze in view of Illum (WO 97/20576)(hereinafter "Illum").

Applicants respectfully submit that the amendments to the claims overcome the rejection. As explained above, Kotze fails to teach or suggest a polycationic carbohydrate, wherein the polycationic carbohydrate possesses a degree of **quaternization** that is at least **20%**. In addition, Claim 1 is amended to clarify that the composition comprises a **biologically active agent** that is capable of generating a **protective immune response** in an animal and a polycationic carbohydrate possessing at least **20% quaternization**.

Applicants submit that, based on the teachings of Kotze, one skilled in the art would lack the motivation to derive a composition comprising a polycationic carbohydrate of at least 20% quaternization because Kotze reports that a **trimethyl chitosan with 40-60% quaternization is an unsuitable absorption enhancer** on the basis that the hydroxyl groups of the chitosan show a high extent of methylation (see page 1199, "Results" column entitled, "Synthesis and Characterization of TMC", last 7 lines of paragraph). Applicants respectfully submit that one of ordinary skill in the art based on the teachings of Kotze would not, therefore, be motivated to combine a biologically active agent capable of generating an immune response in an animal with a polycationic carbohydrate having at least 20% quaternization, as claimed in the amended claims.

Claims 3, 5, 6, 11-12, 20-21 and 37 depend directly or indirectly from Claim 1. As discussed above, applicants respectfully submit that the compositions of the instant application are novel and non-obvious over the teachings of Kotze. Furthermore, the deficiencies of Kotze are not satisfied by Illum for at least the following reasons.

Illum discloses the use of chitosan glutamate as an adjuvant in an intranasal vaccine. Combining the teachings of Illum with Kotze would simply motivate one of ordinary skill in the art to substitute trimethyl chitosan for chitosan glutamate and, for the reasons set out above,

would **teach away** from using trimethyl chitosans with a degree of quaternization that is at least 20%.

Accordingly, applicants respectfully submit that Illum and Kotze fail to provide a case of *prima facie* obviousness because neither Illum or Kotze teach or suggest the compositions as instantly claimed. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

In the Non-Final Office Action mailed October 3, 2006, the Examiner rejected Claims 1, 3-6, 11-12, 20-22 and 37 under 35 U.S.C. §103(a), as being unpatentable over Kotze in view of Duncan *et al.*, (WO 94/20070) (hereinafter "Duncan"). Applicants respectfully submit that amendments to the claims overcome the rejection.

As explained above, Kotze fails to teach or suggest a polycationic carbohydrate having a degree of **quaternization** of at least **20%**. In addition, Claim 1 is amended to clarify that the composition comprises a **biologically active agent** capable of generating a **protective immune response** in an animal and a polycationic carbohydrate possessing at least **20% quaternization**.

Applicants submit that, based on the teachings of Kotze, one of ordinary skill in the art would lack the motivation to derive a composition comprising a polycationic carbohydrate of at least 20% quaternization because Kotze reports that a trimethyl chitosan with 40-60% quaternization is an **unsuitable** absorption enhancer (see page 1199, "Results" column entitled, "Synthesis and Characterization of TMC", last 7 lines of paragraph).

In addition, Claims 3, 5-6, 11-12, 20-22 and 37 depend directly or indirectly from Claim 1. As discussed above, applicants respectfully submit that the compositions of the instant application are novel and non-obvious over the teachings of Kotze. Furthermore, the deficiencies of Kotze are not satisfied by Duncan for at least the following reasons.

Duncan teaches that antigens are more effective when combined with adjuvants and mucoadhesives. Duncan, therefore teaches compositions that produce enhanced immune responses. Applicants assert there would be no motivation for one of ordinary skill in the art to combine the teachings of Duncan with the teachings of Kotze, in the absence of hindsight. Even

so, the fact that Kotze **teaches away** from chitosans having degree of quaternization greater than 20% means that a combination of the teachings would fail to lead to the claimed composition.

Accordingly, applicants respectfully submit that Kotze and Duncan fail to make the claimed composition *prima facie* obvious because neither Kotze nor Duncan teach or suggest the compositions as claimed. Applicants respectfully submit they have overcome the Examiner's rejection under 35 U.S.C. §103(a) and request its withdrawal.

CONCLUSION

Based upon the amendments and remarks provided above, applicants believe that the pending claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned agent at (404) 815-6500 is respectfully solicited.

Respectfully submitted,



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